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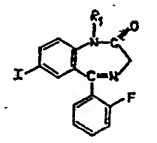
(72) Inventors GEORGE FRANCIS FIELD and LEO HENRYK STERNBACH

(54) BENZODIAZEPINE DERIVATIVES

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with benzodiazepine derivatives. More particularly, the invention is concerned with iodo-substituted benzodiazepine derivatives and a process for the manufacture thereof.

The iodo-substituted benzodiazepine derivatives provided by this invention are compounds of the general formula



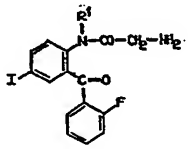
(I)

wherein R_1 represents a hydrogen atom or the methyl group,

and acid addition salts thereof.

According to the process provided by the invention, the iodo-substituted benzodiazepine derivatives aforesaid are manufactured by

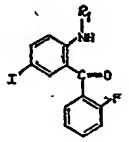
a) cyclising a compound of the general formula



(II)

wherein R_1 has the significance given earlier, or

b) treating a compound of the general formula

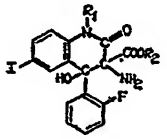


(III)

wherein R_1 has the significance given earlier,

with glycine or an ester thereof or

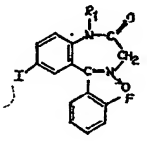
c) effecting ring expansion and acid hydrolysis under aqueous conditions of a compound of the general formula



(IV)

wherein R_1 has the significance given earlier and R_2 represents a lower (C_1—C_4) alkyl group, or

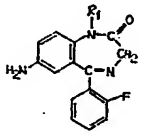
d) deoxidizing a compound of the general formula



(V)

wherein R_1 has the significance given earlier, or

e) subjecting the diazonium salt of a compound of the general formula

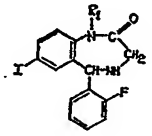


(VI)

wherein R_1 has the significance given earlier,

to a SANDMEYER-type replacement or

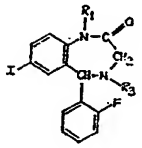
f) oxidising or dehydrogenating at the 4,5-bond a compound of the general formula



(VII)

wherein R_1 has the significance given earlier, or

g) converting a compound of the general formula

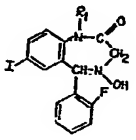


(VIII)

wherein R_1 has the significance given earlier and R_3 represents a halogen atom or an acyl group

into a corresponding 4,5-dehydro compound of formula I by treatment with a strong base or

h) dehydrating a compound of the general formula

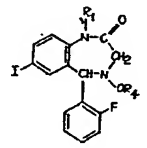


(IX)

wherein R_1 has the significance given earlier,

to yield a corresponding 4,5-dehydro compound of formula I or

i) treating a compound of the general formula

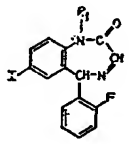


(X)

wherein R_1 has the significance given earlier and R_4 represents an acyl group,

with a base to yield a corresponding 4,5-dehydro compound of formula I or

j) rearranging a compound of the general formula

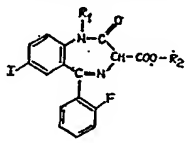


(XI)

wherein R_1 has the significance given earlier,

to a corresponding 4,5-dehydro compound of formula I or

k) saponifying and decarboxylating a compound of the general formula



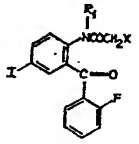
(XII)

wherein R_1 and R_2 have the significance given earlier, or

l) methylating the compound of formula I wherein R_1 represents a hydrogen atom to yield the compound of formula I wherein R_1 represents the methyl group and, if desired,

m) converting a compound of formula I into an acid addition salt.

Thus, in one embodiment of the process of the present invention, the compounds of formula I may be manufactured by cyclising a compound of formula II which, in turn, can be prepared starting from a compound of the general formula



(XIII)

wherein R_1 has the significance given earlier and X represents a leaving atom or group; for example, a halogen atom such as chlorine, bromine or iodine atom, (most preferably a bromo atom), an alkyl or arylsulfonyloxy group (e.g. mesyloxy and tosyloxy), a carbobenzoxy-amino group or a phthalimido group.

The compound of formula II is preferably not isolated but can be cyclised *in situ* under the cyclisation conditions employed to yield the desired compound of formula I directly. Alternatively, the compound of formula II can be isolated and then subsequently ring-closed to the desired compound of formula I. Suitably the cyclisation is readily effected by slight heating of the compound of formula II which is preferably dispersed in an inert organic solvent.

When compounds of formula XIII wherein X represents a halogen atom or an alkyl-sulfonyloxy or arylsulfonyloxy group are used as the pre-starting materials, the cyclisation is effected in the presence of ammonia. This cyclisation is expediently effected utilizing a temperature in the range of from about minus 35°C to 100°C, most preferably in the range of from about minus 35°C to 35°C. The cyclisation may be conducted in the presence of an inert solvent. Suitable solvents for this purpose include inert organic solvents such a slower alkanols (e.g. methanol, ethanol and the like), ethers such as ethyl ether, tetrahydrofuran, ethylene glycol dimethyl ether and the like, chlorinated hydrocarbons such as methylene chloride and the like, and pyridine.

When compounds of formula XIII wherein X represents a carbobenzoxyamino group are used as the pre-starting materials, the cyclisation is effected by first removing the amino-protecting group, for example, by treating a compound of formula XIII with hydrogen bromide in acetic acid to yield a salt of the compound of formula II. This salt is then cyclised to a compound of formula I by making the mixture alkaline. This cyclisation is expediently effected in the presence of an inert solvent. Suitable solvents include those mentioned earlier for the cyclisation of a compound of formula XIII in the presence of ammonia.

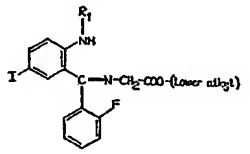
When compounds of formula XIII wherein X represents a phthalimido group are used as the pre-starting materials, the cyclisation is effected by treating said compounds with hydrazine hydrate. Again, this cyclisation is preferably effected in the presence of an inert organic solvent.

In another embodiment of the process of the present invention, the compounds of formula 1 may be manufactured by treating under slightly acidic conditions a compound of formula III with glycine or an ester thereof, with the methyl or ethyl ester being preferred.

In a preferred aspect of this embodiment, a compound of formula III is treated under slightly acidic conditions with a glycine ester of the formula

NH_2CH_2COO—(lower (C_1—C_4) alkyl) (XVI)

to obtain a compound of the formula



(XVII)

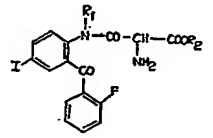
wherein R_1 has the significance given earlier,

which cyclises *in situ* to the desired compound of formula I.

In effecting the aforementioned treatment of a compound of formula III with an ester of glycine, it is preferable to use the hydrochloride of the ester. This treatment is expediently effected in the presence of an inert solvent such as an alcohol containing at least a 3 carbon atom chain such as propanol, butanol and the like or an aromatic hydrocarbon such as benzene, toluene, xylene and the like. Suitable acids for the purpose of rendering the mixture slightly acidic include pivalic acid and p-toluenesulfonic acid. The treatment is preferably effected at elevated temperatures, most preferably at the reflux temperature of the medium.

In a further embodiment of the process of the present invention, the compounds of formula I may be manufactured by effecting ring expansion and acid hydrolysis under aqueous conditions of a compound of formula IV.

Compounds of formula IV can in part, be present in the form of the corresponding isomeric open compounds of the general formula



(IVa)

wherein R_1 and R_2 have the significance given earlier.

Compounds of formula IV can also be converted into corresponding compounds of formula I without isolation from the medium in which they are prepared.

This embodiment of the process is expediently carried out in the presence of

any inert organic solvent. Suitable inert organic solvents for this purpose include aromatic hydrocarbons such as benzene, toluene and the like and chlorinated hydrocarbons such as chloroform, carbon tetrachloride and the like. Temperature and pressure are not critical to the successful performance of this embodiment. Thus, it can be conducted at temperatures from about room temperature to about reflux temperature of the mixture, but is preferably effected with the application of heat, most preferably at about the reflux temperature of the mixture. Suitable acids for the purpose of this embodiment of the process include organic and inorganic acids; for example, alkane carboxylic acids such as formic acid, acetic acid, propionic acid and the like, aromatic acids such as benzoic acid, hydrohalic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid and the like. The amount of acid is not critical, but a complete protonation of the amine nitrogen atom in the starting material should be avoided. When using acetic acid, this can also serve as the solvent.

In a further embodiment of the process of the present invention, compounds of formula I may be manufactured by deoxidizing a compound of formula V.

The deoxidation of a compound of formula V can be carried out by treatment with a phosphorus trihalide such as phosphorus trichloride. This deoxidation is expediently carried out in the presence of an organic solvent such as an aromatic hydrocarbon (e.g. benzene, toluene and the like) or a chlorinated hydrocarbon (e.g. carbon tetrachloride and the like) and at room temperature, although temperatures above and below room temperature can likewise be employed.

Alternatively, the deoxidation of a compound of formula V can be carried out by hydrogenation in the presence of a hydrogenation catalyst such as RANEY-nickel. The hydrogenation is expediently effected in the presence of an inert organic solvent such as dioxane, dimethoxyethane, ethyl acetate and the like at room temperature, although temperatures above and below room temperture can also be employed. In addition, the hydrogenation can be carried out under pressure.

Furthermore, the deoxidation can be effected by treating a compound of formula V with zinc in a small amount of acetic acid. This treatment is expediently effected at room temperature in the presence of an inert organic solvent such as methylene chloride.

In a further embodiment of the process of the present invention, compounds of formula I may be manufactured from the corresponding 7 - amino - 1,4 - benzodiazepin - 2 - ones using a SANDMEYER-type replacement. In effecting this embodiment there is first formed the diazonium salt of a compound of the formula VI above.

The amino group of the compound of formula VI may be diazotized using conventional techniques; for instance, by treatment with any combination of reagents that produces *in situ* nitrous acid such as, for example, sodium nitrite in a mineral acid (e.g. hydrochloric acid or sulfuric acid). The diazonium salt of a compound of formula VI is then reacted with an iodide salt, preferably an alkaline metal iodide such as sodium iodide or potassium iodide, or cuprous iodide, to yield the compound of formula I.

The diazotization of a compound of formula VI is, as mentioned earlier, carried out according to standard procedures. For example, the compound of formula VI is dissolved in an aqueous solution of a mineral acid and the mixture is cooled to a temperature between 0°C and minus 10°C. An aqueous solution of sodium nitrite is then added slowly to form the diazonium salt. To avoid decomposition, the salt is then immediately reacted with the iodide salt to effect displacement and formation of the iodo compound.

In a further embodiment of the process of the present invention, compounds of formula I may be manufactured by dehydrogenating or oxidizing a compound of formula VII.

The dehydrogenation or oxidation of a compound of formula VII can, for example, be effected with oxygen, manganese dioxide, bromine, chlorine, azodicarboxylic acid esters (e.g. the diethyl ester) and the like. Preferred oxidizing agents for the purposes of this embodiment of the process are bromine and diethyl azodicarboxylate. This embodiment is expediently carried out in the presence of an inert organic solvent such as an aromatic hydrocarbon (e.g. benzene, toluene and the like) a halogenated hydrocarbon (e.g. carbon tetrachloride), an alcohol (e.g. methanol, ethanol and the like), an ether (e.g. dioxane, tetrahydrofuran and the like), advantageously at a temperature between about minus 40°C and the reflux temperature of the solvent.

When a halogen such as bromine or chlorine is employed as the oxidizing agent, there may be formed as an intermediate product a compound of formula VIII wherein R_2 represents a halogen atom such as a chlorine or bromine atom. Such intermediate product can be converted into a corresponding 4,5-dehydro compound of formula I by treatment with a strong base.

In a further embodiment of the process of the present invention, a compound of formula VIII is converted into the corresponding 4,5-dehydro compound of formula

I by treatment with a strong base. Examples of acyl groups denoted by R_3 in compounds of formula VIII are alkylsulfonyl groups (e.g. mesyl) and arylsulfonyl groups (e.g. tosyl).

The splitting off of the R_3 substituent from a compound of formula VIII can be achieved by treatment with a strong base such as an alkali hydride (e.g. sodium hydride), an alkali alkoxide (e.g. sodium methoxide and potassium *tert*butoxide), triethylamine and alkali amides (e.g. sodium amide), all of which should be used in anhydrous medium. This treatment is expediently carried out in the presence of an inert organic solvent. Suitable solvents for this purpose include ethers, alcohols (e.g. ethanol), hydrocarbons (e.g. benzene and toluene) and dimethylformamide. The treatment is preferably effected using temperatures between about 0°C and about 120°C. In this embodiment of the process there may be formed as an intermediate product a compound of formula XI which can be rearraged to a corresponding 4,5-dehydro compound of formula I by treatment with a base.

In a further embodiment of the process of the present invention, a compound of formula IX is dehydrated to yield a compound of formula I.

The dehydration (i.e. splitting out of water) of a compound of formula IX can be effected with any suitable reagent that will effect dehydration of the compound; for example, thionyl chloride, phosphorus oxychloride and carbodiimides such as di*cyclo*hexylcarbodiimide. This dehydration is expediently effected at room temperature and in the presence of an inert organic solvent such as a hydrocarbon, an alcohol and the like. In this embodiment of the process, there may be formed as an intermediate product a compound of formula XI which can be rearranged to a corresponding 4,5-dehydro compound of formula I by treatment with a base.

In a further embodiment of the process of the present invention, a compound of general formula X is treated with a base to yield a corresponding 4,5-dehydro compound of formula I.

The acid cleavage of a compound of formula X can be achieved with a strong base. Suitable bases include alkali hydrides such as sodium hydride, triethyl amine, alkali amides such as sodium amide, alkali alkoxides such as sodium methoxide and potassium *tert*butoxide, all of which are used in an anhydrous medium. This treatment is expediently effected in the presence of an inert organic solvent such as an ether, an alcohol (e.g. ethanol), a hydrocarbon (e.g. benzene and toluene), dimethylformamide and the like and at temperatures between about minus 40°C and about 120°C. The acyl group present as the R_4 substituent can be a lower (C_2—C_4) alkanoyl group such as acetyl, an aroyl group such as benzoyl, a lower (C_1—C_4) alkylsulfonyl group such as mesyl or an arylsulfonyl group such as tosyl.

In the acid cleavage of a compound of formula X there may be formed as an intermediate product a compound of formula XI which can be rearranged to a corresponding 4,5-dehydro compound of formula I by treatment with a base.

In a further embodiment of the process of the present invention, a compound of formula XI can be rearranged to a corresponding 4,5-dehydro compound of formula I by treatment with a base such as an alkali alkoxide (e.g. sodium methoxide), an alkali hydride (e.g. sodium hydride), triethylamine and the like. The treatment is expediently effected in an inert organic solvent such as a hydrocarbon, an ether, an alcohol and the like and at temperatures between about minus 40° and 120°C.

In a further embodiment of the process of the present invention, compounds of formula I can be manufactured by saponifying and decarboxylating a compound of formula XII.

The compounds of formula XII can be saponified using conventional techniques to yield the corresponding compounds wherein the substituent in the 3-position is the group —COOA in which A represents the cation of a base. For example, the saponification of a compound of formula XII can be effected by treatment with a base such as an alkali hydroxide (e.g. sodium hydroxide, potassium hydroxide and the like), an alkaline earth hydroxide (e.g. calcium hydroxide and the like), a tertiary organic base such as triethylamine and the like or ethanolamine. The saponification of a compound of formula XII can also be effected by treatment with an acid. When an acid is used, saponification and decarboxylation may occur simultaneously so as to produce a compound of formula I.

Following the saponification, the resulting compound is decarboxylated using conventional techniques to give the desired compound of formula I. The decarboxylation can be accomplished simply by allowing a solution of the saponification product to stand or by heating or acidifying this product in solution. This decarboxylation occurs slowly upon standing, more quickly on heating and spontaneously upon acidification.

In a further embodiment of the process of the present invention, the compound of formula I wherein R_1 represents the methyl group can be manufactured from the corresponding des-methyl compound by methods known in the art. For example, the 1-position can be methylated by conventional techniques. Thus, for example, the compound of formula I wherein R_1 represents a hydrogen atom is

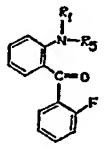
treated with an alkali metal hydride (e.g. sodium hydride), potassium tertbutoxide and the like to form the 1-alkali metal salt of said compound and thereafter the 1-alkali metal salt is treated with a methylating agent such as methyl halide (e.g. methyl iodide) or dimethyl sulfate to form the 1-methyl compound.

The methylation is preferably effected in the presence of an inert organic solvent such as tetrahydrofuran. Temperature and pressure are not critical, but for the sake of convenience the methylation is preferably effected at room temperature and atmospheric pressure.

The compounds of formula I can be converted into acid addition salts, particularly into pharmaceutically acceptable acid addition salts, with both organic and inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, succinic acid, methanesulfonic acid, *p*-toluenesulfonic acid and the like. The pharmaceutically acceptable acid addition salts may be formed following conventional techniques.

The starting materials required in the process of the present invention may be prepared by several different procedures.

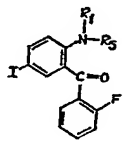
In one such procedure, a compound of the formula



(XV)

wherein R_1 has the significance given earlier and R_2 represents a hydrogen atom or the acetyl group or a group of the formula $-COCH_2X$ in which X has the significance given earlier,

is treated with iodine monochloride in the presence of an inert organic solvent to yield the desired iodinated benzophenone of the formula



(XIV)

wherein R_1 and R_2 have the significance given earlier.

The treatment of a compound of formula XV with iodine monochloride is preferably effected in the presence of an inert organic solvent. Suitable solvents for this purpose include alcohols such as methanol, ethanol and the like, hydrocarbons such as benzene, toluene and the like, halogenated hydrocarbons such as chloroform, carbon tetrachloride and the like, acetic acid and glacial acetic acid. In a preferred aspect, either chloroform, acetic acid or glacial acetic acid is used as the solvent.

The conditions employed in treating a compound of formula XV with iodine monochloride may be varied since temperature, pressure and time are not critical to the process. Thus, temperatures within a range of from about 10°C to about 100°C are suitable, with the choice of the preferred temperature depending primarily upon the solvent system employed. Thus, for instance, if chloroform is used as the solvent, the treatment is expediently effected at room temperature, while if either acetic acid or glacial acetic acid is used as the solvent, the treatment is expediently effected at elevated temperatures, preferably between about 60°C and 100°C, most preferably at about 80°C. Likewise, for the sake of convenience, the treatment is preferably effected at atmospheric pressure.

The molar ratios of the component of formula XV and iodine monochloride in the foregoing treatment will vary somewhat with the choice of the compound of formula XV, the conditions under which the treatment is carried out and, especially, the solvent in which the treatment is conducted. Since mono-iodination is desired, where chloroform is usel as the solvent it is preferable to utilize 2 moles of iodine monochloride in the treatment since this molar ratio results in optimum yields. On the other hand, if in the same circumstances acetic acid is used as the solvent, it is preferable to use one mole of iodine monochloride.

Where a compound of formula XV in which R_2 represents a halo-acetyl group is treated with iodine monochloride, the treatment may, in addition to iodinating the benzophenone, also bring about a halogen exchange in the halo-acetyl group; that is to say, the chlorine, bromine or fluorine atom present in the halo-acetyl group may be replaced by the more reactive iodine atom.

Alternatively, the compounds of formula XIV may be prepared by treating a compound of formula XV with iodine in the presence of a suitable oxidizing agent.

In effecting the iodination of a compound of formula XV with iodine, any suitable oxidizing agent may be employed. Examples of oxidizing agents which can be utilized for this purpose include sodium persulfate, nitric acid, iodic acid, mercuric oxide, lead oxide, silver oxide and the like. In a preferred

embodiment, sodium persulfate is employed as the oxidizing agent.

It is probable that the iodination of a compound of formula XV with iodine under oxidizing conditions is the result of the removal of the iodide ion formed as a by-product in the treatment by oxidation. Thus any oxidizing agent which oxidizes the hydroiodic acid or iodide ion so formed in the reaction to iodine is suitable for the present purposes. While the aforementioned oxidizing agents are examples of preferred embodiments, it will be appreciated that any suitable oxidizing agent can be used. All that is required of the oxidizing agent is that it promote the formation of iodine under the conditions employed.

Where a compound of formula XV in which R_5 represents a halo-acetyl group is treated with iodine under oxidizing conditions, the treatment may, in addition to iodinating the benzophenone, also bring about a halogen exchange in the halo-acetyl group; that is to say, the chlorine, bromine or fluorine atom present in the halo-acetyl group may be replaced by the more reactive iodine atom.

The treatment of a compound of formula XV with iodine under oxidizing conditions is preferably effected in the presence of an inert organic solvent. Suitable solvents for this purpose include alcohols such as methanol, ethanol and the like, hydrocarbons such as benzene, toluene and the like, halogenated hydrocarbons such as chloroform, carbon tetrachloride and the like, acetone, ether, petroleum ether, carbon disulfide and glacial acetic acid. In a preferred aspect, glacial acetic acid is employed as the solvent.

The conditions employed in iodinating a compound of formula XV with iodine in the presence of an oxidizing agent may be varied since temperature, pressure and time are not critical to the process. Thus, temperatures within a range of from about 10°C to about 100°C are suitable. However, for optimum yields, temperatures above room temperature are preferably employed. Likewise times (usually between 12 and 36 hours) which permit completion of the treatment are utilized. For the sake of convenience, the treatment is effected at atmospheric pressure.

The compounds of formula XIV and processes for their preparation which comprise treating a compound of the formula XV with iodine monochloride or with iodine in the presence of an oxidizing agent are described and claimed in Copending Applications Nos. 12290/72 (Serial No. 1332698) and 12291/72 (Serial No. 1332699).

The compounds of formula XV hereinbefore are known compounds or can be prepared in analogy to the preparation of known compounds.

If, in the compounds of formula XIV, R_5 represents a hydrogen atom, these compounds can be converted to the compounds of formula XIII by reaction with a compound of the formula

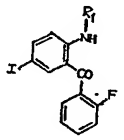
$$X'—CO—CH_2—X \qquad (XVIII)$$

wherein X′ represents a halogen atom and X has the significance given earlier.

When R_5 in the compounds of formula XIV represents an acetyl group, conversion to the compounds of formula XIII may be accomplished by removing the acetyl group therefrom by hydrolysis and reacting the resulting compound with a compound of formula XVIII hereinbefore.

2′ - Fluoro - 5 - iodo - 2 - methylaminobenzophenone may be prepared from 2 - amino - 2′ - fluoro - 5 - iodobenzophenone by tosylation, methylation and splitting off of the tosyl group by acid hydrolysis.

Compounds of formula IV can be prepared by reacting a benzophenone of the general formula



(XIX)

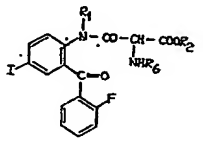
wherein R_1 has the significance given earlier,

with a compound of the general formula

$$X'—CO—\underset{\displaystyle NHR_6}{\underset{|}{CH}}—COOR_2 \qquad (XX)$$

wherein R_2 and X′ have the significance given earlier and R_6 represents a carbobenzoxy group,

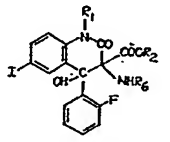
and treating a so-obtained compound of the general formula



(XXI)

wherein R_1, R_2 and R_6 have the significance given earlier,

either with a hydrohalic acid such as hydrobromic acid and glacial acetic acid or with a base and then treating a resulting compound of the general formula



(XXII)

wherein R_1, R_2 and R_6 have the significance given earlier,

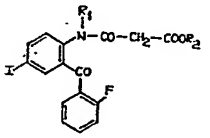
with a hydrohalic acid.

Compounds of formula IV can also be prepared by reacting a benzophenone of formula XIX with a compound of the general formula

$$X'—CO—CH_2—COOR_2 \quad (XXIII)$$

wherein R_2 and X' have the significance given earlier,

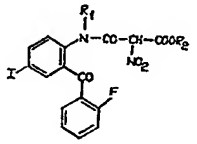
nitrating or nitrosating a so-obtained compound of the general formula



(XXIV)

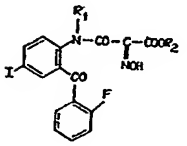
wherein R_1 and R_2 have the significance given earlier,

and reducing a resulting compound of the general formula



(XXVa)

or

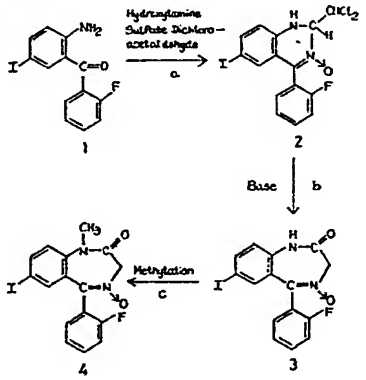


(XXVb)

wherein R_1 and R_2 have the significance given earlier.

The compounds of formula V may be prepared following the procedures depicted in formula scheme A hereinafter:

Formula Scheme A

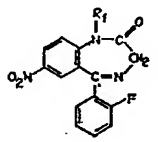


Having regard to formula scheme A, step (a) is expediently effected in the presence of an inert organic solvent; for example, an alcohol such as methanol, ethanol and the like.

The conversion of the quinazoline compound 2 to the benzodiazepine compound 3 (step b) is effected by treatment with a base. Suitable bases for this purpose include alkali metal hydroxides such as sodium hydroxide and potassium hydroxide. This treatment is preferably effected in the presence of an inert organic solvent such as ethanol.

The optional step (c) of methylating the benzodiazepine compound 3 to the benzodiazepine compound 4 can be effected following the methylation procedures described earlier.

Compounds of formula VI can be prepared by reducing a corresponding 7-nitro compound of the general formula



(XXVI)

wherein R_1 has the significance given earlier,

for example, with stannous chloride in aqueous hydrochloric acid.

The compounds of formula VII may be prepared by the deoxidation and reduction of a compound of formula V using an excess of zinc in acetic acid.

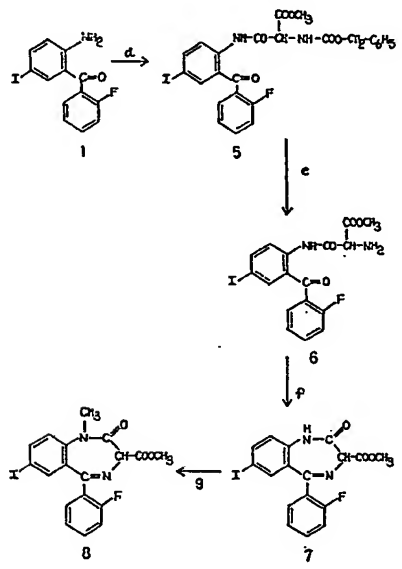
Compounds of formula VIII wherein R_3 represents an acyl group can be prepared by treating a compound of formula VII with an appropriate acylating agent.

The compounds of formula IX may be prepared by treatment of a corresponding compound of formula V with sodium borohydride.

Compounds of formula X can be prepared by treating a compound of formula IX with an appropriate acylating agent.

Compounds of formula XII may be prepared following the procedures depicted in formula scheme B hereinafter which shows the preparation of compounds of formula XII wherein R_2 represents the methyl group.

Formula Scheme B



Compound 1 is converted into compound 5 by reaction with N - benzyloxycarbonyl - 2 - carbomethoxyglycine chloride. Compound 5 is treated with hydrobromic acid in acetic acid to split off the benzyloxycarbonyl group. Compound 6 is cyclized to the benzodiazepine compound 7 which may be methylated to the benzodiazepine compound 8.

The compounds of formula I and their pharmaceutially acceptable acid addition salts are useful as anticonvulsants, muscle relaxants and sedatives. Thus, they can be used as medicaments.

For example, they can be used in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier. This carrier can be an organic or inorganic inert carrier material which is suitable for enteral or parenteral application such as, for example, water, gelatin, lactose, starches, magnesium stearate, talc, vegetable oils, gum arabic, polyalkylene glycols, petroleum jelly, etc. The pharmaceutical preparations can be made up in solid form (e.g. as tablets, dragées, suppositories or capsules) or in liquid form (e.g. as solutions, suspensions or emulsions). They may be sterilized and/or may contain additives such as preserving, stabilizing, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They can also contain other therapeutically valuable substances.

The compounds of formula I or their pharmaceutically acceptable salts can be administered at dosages adjusted to individual requirements and fitted to the pharmaceutical exigencies of the situation. Convenient pharmaceutical dosages are in the range of from about 0.05 mg to about 1 mg per day.

As will be noted from the foregoing, the compounds of formula I and their pharmaceutically acceptable salts are useful as sedatives, muscle relaxants and anticonvulsants. Their usefulness can be observed in a number of tests. These tests were performed using the following compounds of formula I as the test compounds: 5 - (2 - fluorophenyl) - 7 - iodo - 1,3 - dihydro - 1 - methyl - 2H - 1,4 - benzodiazepine - 2 - one (Compound A) and 5 - (2 - fluorophenyl) - 7 - iodo - 1,3 - dihydro - 2H - 1,4 - benzodiazepine - 2 - one (Compound B).

The sedative and muscle relaxant activity of the compounds of the invention can be observed by the results in the following tests:

Inclined Screen Test:

Male mice were given up to a maximum dose of 500 mg/kg *p.o.* and left on the inclined screen at least four hours for observation of paralyzing effects severe enough to cause them to slide off the screen. On the basis of 6 mice/dose and at least 2 points between 100 and 0 per cent, the PD_{50} was calculated by the method of BEHRENS [(Arch. Exp. Pathol. Pharmakol. *140*, 237 (1929)]. In following this test procedure, Compound A exhibited PD_{50} of 1 mg/kg and Compound B exhibited a PD_{50} of 3.5 mg/kg.

Unanaesthesized cat:

Normal cats were treated *p.o.* and observed for gross changes in behaviour. Minimum effective dose (M.E.D.) was the lowest dose at which symptoms were observed. Following these test procedures, compound A exhibited a M.E.D. of 0.05 mg/kg and compound B exhibited a M.E.D. of 0.1 mg/kg.

Foot Shock:

A pair of mice is confined under a one litre beaker placed on a grid which presents shock to the feet. At least 5 fighting episodes are elicited in a 2-minute period. Pairs of mice are marked and pretreated 1 hour prior to a second shocking. Logarithmic dose intervals are utilized up to a maximum of 100 mg/kg. At the 100 per cent blocking dose (PD 100), 3 out of 3 pairs must be blocked from fighting. The measurements are made at the dose level at which 100 per cent blocking is observed and the results are expressed as the dose in mg/kg which block the fighting

response for one hour. Following these test procedures, compound A exhibited a PD_{150} of 1.0 mg/kg and compound B exhibited a PD_{100} of 2 mg/kg.

The anticonvulsant activity of the compounds of the present invention can be demonstrated by the results obtained in the following test:

Maximal Electroshock:

This test was performed according to the method described by SWINYARD, GOODMAN and BROWN [J.Pharmacol. Exp.Ther. *106*, 319 (1952)] with the following modifications. Male mice were used and the shock was delivered in the same form and duration described in the above method. However, 30 mA was delivered as the electroshock instead of 50 mA. One hour after receiving the compound, the animals were shocked to note any anti-convulsant effects. Prevention of tonic hind limb extension is considered to be the end point of anti-convulsant activity. Following this test procedure, compound A exhibited an ED_{50} of 1.6 mg/kg and compound B exhibited an ED_{50} of 1.3 mg/kg.

7 - Halo - 1,4 - benzodiazepin - 2 - ones are known in the art. However, prior to the invention of the compounds of formula I, no one has recognized the particular efficacious capability of the 5 - (2 - fluorophenyl) - 7 - iodo - 1,4 - benzodiazepin - 2 - one compounds of formula I to function as a sedative, muscle relaxant and anti-convulsant, thus rendering them eminently useful as transquilizing agents. The discovery of these heretofore undisclosed compounds and their unusual ability to function as particularly efficacious sedatives constitutes the major part of the present invention.

The following Examples illustrate the present invention. All temperatures are given in degrees Centigrade.

Example 1

A mixture of 27 g. (58.5 mmole) of 2 - bromo - 2′ - (2 - fluorobenzoyl) - 4′ - iodoacetanilide and 750 ml of liquid ammonia was stirred under a dry ice condenser for 5 hours and the ammonia was allowed to evaporate overnight. The residue was heated under reflux with 1.2 litres of pyridine with stirring for 2 hours. The pyridine was distilled off *in vacuo* and the residue partitioned between methylene chloride and water. The residue from the dried (sodium sulfate) organic phase was crystallized from ether to give 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 2H - 1,4 - benzodiazepin - 2 - one of melting point 221°—223°. Recrystallization from ethanol gave colourless needles of melting point 222°—224°. During this reaction, 2 - amino - 2′ - (2 - fluorobenzoyl) - 4′ - iodoacetanilide is formed as an intermediate without being isolated.

The starting material can be prepared as follows:

To a stirred solution of 43 g (0.2 mole) of 2 - amino - 2′ - fluorobenzophenone in 1 litre of chloroform were added 65 g (0.4 mole) of iodine monochloride in 50 ml of chloroform at room temperature. This mixture was stirred for 1 hour at room temperature and the excess iodine monochloride was destroyed by the addition of 1 litre of saturated sodium bisulfite solution. The mixture was then neutralized with concentrated ammonium hydroxide. The chloroform layer was separated, dried over sodium sulfate and concentrated *in vacuo*. The residue crystallized with hexane to give 2 - amino - 2′ fluoro - 5 - iodobenzophenone of melting point 93°—96°. Recrystallization from ethanol/water gave orange needles of melting point 102°—105°.

A mixture of 32.1 g (94.3 mmole) of 2 - amino - 2′ - fluoro - 5 - iodobenzophenone, 40.2 g (0.2 mole) of bromoacetyl bromide and 500 ml of benzene was heated under reflux for 2 hours, cooled and neutralized with dilute ammonium hydroxide. Methylene chloride was added and the organic phase was separated. It was washed with water, dried over sodium sulfate and concentrated in vacuo to 200—300 ml. Addition of petroleum ether gave 2 - bromo - 2′ - (2 - fluorobenzoyl) - 4′ - iodoacetanilide of melting point 148°—151°. Recrystallization from ethanol gave off-white needles of melting point 150°—151°.

2 - Amino - 2′ - fluoro - 5 - iodobenzophenone may also be prepared as follows:

A mixture of 12 g (55 moles) of 2 - amino - 2′ - fluorobenzophenone, 125 ml of glacial acetic acid, 12.7 g (50 mmole) of iodine and 47.6 g (200 mmole) of sodium persulfate was stirred at 20°—25° for 3 days. It was diluted with 500 ml of water and extracted with three 100 ml portions of methylene chloride. The combined organic phases were shaken with 200 ml of 10% sodium bisulfite solution. The aqueous phase was made basic with concentrated ammonium hydroxide and shaken again with the organic phase. The organic phase was separated, dried over sodium sulfate and concentrate *in vacuo*. The residue was crystallized from hexane to give crude 2 - amino - 2′ - fluoro - 5 - iodobenzophenone. Recrystallization from ethanol/water mixtures gave a pure sample of melting point 102°—105°.

Example 2

A mixture of 1 g of 2 - bromo - 2′ - (2 - fluorobenzoyl) - 4′ - iodo - N - methylacetanilide, 10 ml of dimethylformamide and

2 ml of concentrated aqueous ammonia was heated to reflux for 3 minutes. The cooled solution was diluted with water and extracted with ether. The combined extracts were washed with water, dried over sodium sulfate and evaporated. Chromatography of the residue on 8 g of silica gel using (ethyl acetate)/(methylene chloride) (1:1) yielded 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one with a melting point of 106°—109° after crystallization from ether/hexane. During this reaction, 2 - amino - 2′ - (2 - fluorobenzoyl) - 4′ - iodo - N - methylacetanilide is formed as an intermediate without being ioslated.

The starting material can be prepared as follows:

A mixture of 34.1 g (0.1 mole) of 2 - amino - 2′ - fluoro - 5 - iodobenzophenone, 22.9 g (0.12 mole) of *p* - toluenesulfonyl chloride and 250 ml of dry pyridine was heated under reflux for 1 hours and concentrated *in vacuo*. To the residue were added 500 ml of methylene chloride and 500 ml of water. The pH of the aqueous layer was adjusted to 7 with concentrated ammonium hydroxide. The methylene chloride layer was separated, dried over sodium sulfate and filtered through 300 g of alumina using 1 litre of methylene chloride to elute. The eluate was concentrated *in vacuo* and the residue was crystallized from ether to give 2′ - (2 - fluorobenzoyl) - 4′ - iodo - *p* - toluenesulfonanilide of melting point 146°—149°. For further purification, 1 g was dissolved in methylene chloride and the solution filtered through 20 g of alumina. The residue left on concentration of the eluate was crystallized from ether and then recrystallized by distilling the methylene chloride from a solution in methanol and methylene chloride to give off-white prisms of melting point 151°—153°.

To a solution of 9.9 g (0.02 mole) of 2′ - (2 - fluorobenzoyl) - 4′ - iodo - *p* - toluenesulfonanilide in 125 ml of dry dimethylformamide was added 0.6 g (0.0125 mole) of sodium hydride (50% mineral oil). After the mixture had been stirred for 10 minutes, 1.87 ml (0.03 mole) of methyl iodide were added. The mixture was stirred for 18 hours at room temperature and poured into 300 ml of water and 75 ml of ether. The solid was collected to give crude 2′ - (2 - fluorobenzoyl) - 4′ - iodo - N - methyl - *p* - toluenesulfonanilide of melting point 162°—164°. Recrystallization from chloroform/(petroleum ether) gave colourless prisms of melting point 146°—148°

To 100 ml of 70% sulfuric acid heated to 105° were added 5 g of 2′ - (2 - fluorobenzoyl) - 4′ - iodo - N - methyl - *p* - toluenesulfonanilide. The temperature was raised to 145° in about 10 minutes. At 125° purple fumes began to be given off, indicating the loss of iodine. The solution was poured on to 1 kg of crushed ice. The mixture was extracted with three 250 ml portions of methylene chloride. The extracts were dried over sodium sulfate and concentrated to dryness *in vacuo*. The residue was crystallized from 100 ml of boiling hexane to give crude 2′ - fluoro - 5 - iodo - 2 - methylaminobenzophenone of melting point 93°—96°. Recrystallization from hexane gave yellow needles of melting point 97°—100°.

A mixture of 3.6 g of 2′ - fluoro - 5 - iodo - 2 - methylaminobenzophenone, 30 ml of methylene chloride and 3 g of bromoacetyl bromide was stirred at room temperature for 1 hour, washed with water and saturated sodium bicarbonate solution, dried over sodium sulfate and evaporated. The residue was crystallized from methanol and recrystallized from (methylene chloride)/hexane to yield 2 - bromo - 2′ - (2 - fluorobenzoyl) - 4′ - iodo - N - methyl - acetanilide with a melting point of 90°—93°.

Example 3

A solution of 16.2 g (40 mmole) of 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 2H - 1,4 - benzodiazepin - 2 - one in 500 ml of dry tetrahydrofuran was treated with 6.72 g (60 mmole) of potassium *tert*-butoxide and then with 11.4 g (80 mmole) of methyl iodide and the mixture was stirred overnight at room temperature. The mixture was filtered through diatomaceous silica and the filtrate concentrated *in vacuo*. The residue was dissolved in 650 ml of ether. After the solution had been filtered, it was saturated with dry hydrogen chloride. The product was collected and recrystallized from methanol/ether to yield 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one hydrochloride of melting point 226°—229° as yellow prisms.

A mixture of 5 g of the foregoing hydrochloride, 200 ml 10% sodium carbonate solution and 200 ml of ether was shaken. The ether layer was separated, dried over sodium sulfate and concentrated *in vacuo*. The residue was crystallized from ether/(petroleum ether) to yield the free base of melting point 107°—115°. Recrystallization from ether/(petroleum ether) gave colourless prisms of melting point 107°—110°.

Example 4

A mixture of 0.9 g of 2′ - fluoro - 5 - iodo - 2 - methylaminobenzophenone, 0.9 g of glycine ethyl ester hydrochloride, 3 g of pivalic acid and 30 ml of toluene was refluxed for 48 hours with distillation of part of the solvent. 15 ml of toluene were distilled off and replaced in the beginning and, after 24 hours, the cooled reaction mixture was par-

titioned between toluene and 10% aqueous sodium carbonate solution. The organic layer was washed with sodium carbonate solution and water, dried over sodium sulfate and evaporated. The residue was chromatographed on 20 g of silicagel using methylene chloride followed by 20% ethyl acetate in methylene chloride for elution. Crystallization of the pure fractions gave 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one with a melting point of 106°—109°.

Example 5

0.5 g of 3 - amino - 3 - carbomethoxy - 4 - (2 - fluorophenyl) - 1,2,3,4 - tetrahydro - 4 - hydroxy - 6 - iodo - 1 - methylquinolin - 2 - one were boiled in 10 ml of 80% acetic acid for 24 hours. The residue obtained after evaporation in a vacuum was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The methylene chloride phase was dried over sodium sulfate and evaporated. The residue was chromatographed on 8 g of silicagel using 20% ethyl acetate in methylene chloride. Pure fractions were combined and evaporated. Crystallization of the residue from ether/hexane yielded 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 105°—109°.

The starting material was prepared as follows:

A mixture of 8 g of N - (benzyloxycarbonyl) - 2 - carbomethoxy - glycine, 6.3 g of phosphorus pentachloride and 100 ml of methylene chloride was mixed at minus 20° to minus 15° for 45 minutes. 5 g of 2′ - fluoro - 5 - iodo - 2 - methylaminobenzophenone were added and stirring was continued without cooling for 1 hour, 50 ml of water were added and the two phase system was refluxed for 1 hour. The methylene chloride layer was separated, washed with 10% aqueous sodium carbonate, dried over sodium sulfate and evaporated. The residue was dissolved in 50 ml of methanol containing 2 ml of triethylamine. After heating to the boiling point of solution was cooled, whereupon the product crystallized. The collected crystals were recrystallized from (methylene chloride)/hexane to yield 3 - (benzyloxycarbonylamino) - 3 - carbomethoxy - 4 - (2 - fluorophenyl) - 1,2,3,4 - tetrahydro - 4 - hydroxy - 6 - iodo - 1 - methylquinolin - 2 - one of melting point 210°—220° (decomposition).

20 ml of acetic acid containing 30% hydrogen bromide were added to a warm solution of 5 g of the product obtained according to the preceding paragraph in 100 ml of methylene chloride. After standing at room temperature for four hours, the reaction mixture was concentrated under reduced pressure. The residue was crystallized from (methylene chloride)/ether to yield a hydrobromide of melting point 170°—180° decomposition).

4 g. of the foregoing hydrobromide were partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The methylene chloride layer was dried and evaporated. Crystallization of the residue from ether yielded 3 - amino - 3 - carbomethoxy - 4 - (2 - fluorophenyl) - 1,2,3,4 - tetrahydro - 4 - hydroxy - 6 - iodo - 1 - methylquinolin - 2 - one melting at 170°—172° after recrystallization from (ethylene chloride)/hexane.

Example 6

1 ml of phosphorus trichloride was added to a solution of 0.41 g of 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one 4 - oxide in 10 ml of methylene chloride. After standing at room temperature for 30 minutes, the mixture was partitioned between 10% aqueous sodium sulfate and evaporated. Crystallization of the residue from ether/hexane yielded 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 104°—108°.

The starting material may be prepared as follows:

A mixture of 102.3 g of 2 - amino - 2′ - fluoro - 5 - iodo - benzophenone, 24 g of hydroxylamine sulfate, 45 g of dichloroacetaldehyde and 1 litre of ethanol was warmed with stirring to effect solution and was further stirred at room temperature overnight. The mixture was neutralized by addition of saturated sodium bicarbonate solution and diluted with a large volume of water. The precipitated solid was collected, washed with water and dried to give yellow 2 - dichloromethyl - 4 - (2 - fluorophenyl) - 1,2 - dihydro - 6 - iodoquinazoline - 3 - oxide of melting point 184°—187°.

100 ml of 3-*N* aqueous sodium hydroxide were added to a suspension of 45.1 g of 2 - dichloromethyl - 4 - (2 - fluorophenyl) - 1,2 - dihydro - 6 - iodoquinazoline 3 - oxide in 750 ml of ethanol. The mixture was stirred for 2.5 hours at room temperature and then concentrated under reduced pressure. The residue was partitioned between methylene chloride and 1-N aqueous hydrogen chloride. The organic layer was washed with water, dried over sodium sulfate, filtered and evaporated. The residue was crystallized and recrystallized from ethanol to yield 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 2H - 1,4 - benzodiazepin - 2 - one 4 - oxide of melting point 192°—196°.

6.2 g of potassium *tert*butoxide were added to a solution of 19.8 g of 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 2H -

1,4 - benzodiazepin - 2 - one 4 - oxide in 250 ml of tetrahydrofuran cooled to 0° with stirring under nitrogen. After stirring for 1 hour at 0°, 7.8 g of methyl iodide were added and the mixture was stirred for an additional 2 hours without cooling, then filtered and evaporated to dryness. The residue was partitioned between methylene chloride and water. The methylene chloride layer was dried, filtered and evaporated. Crystallization from ethanol yielded 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one 4 - oxides of melting point 178°—181° after recrystallization from ethanol.

Example 7

A solution of 0.33 g of sodium nitrite in 5 ml of water was added to a solution of 1.2 g of 7 - amino - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one in 3.5 ml of 6-*N* hydrochloride acid cooled to 0°. The yellow solution was stirred for 10 minutes at 0° to 5°. A solution of 1.2 g of potassium iodide in 5 ml of water was then added and stirring was continued for 30 minutes at room temperature. After filtration, the filtrate was made alkaline with ammonia and was extracted with methylene chloride. The combined extracts were washed with water, dried over sodium sulfate and evaporated to leave an orange oil. Crystallization from (methylene chloride)/ether/(petroleum ether) yielded 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 102°—107°.

The starting material may be prepared as follows:

A solution of 30 g of stannous chloride dihydrate in 80 ml of 6-*N* hydrochloric acid was added to a solution of 12.5 g of 5 - (2 - fluorophenyl) - 1,3 - dihydro - 1 - methyl - 7 - nitro - 2H - 1,4 - benzo diazepin - 2 - one in 80 of 6-*N* hydrochloric acid. The mixture was stirred overnight and the resulting suspension was made alkaline by addition of 50% aqueous potassium hydroxide. The yellow precipitated solid was collected, washed with water, dried and recrystallized from tetrahydrofuran/hexane to yield 7 - amino - 5 - (2 - fluorophenyl) - 1,3 - dihydro - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 206°—208° (decomposition).

Example 8

A solution of 0.4 g of 5 - (2 - fluorophenyl) - 1,2,3,4 - tetrahydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one in 10 ml of chloroform was cooled to minus 20°. 3.6 ml of a molar solution of bromine in chloroform were added and htirring was continued for 15 minutes at minus 10°. The reaction mixture was partitioned between 1-*N* sodium hydroxide and chloroform. The organic layer was dried and evaporated. The residue was dissolved in 10 ml of methanol and stirred for 10 minutes after addition of 10 mg of sodium methoxide. The mixture was diluted with water and extracted with benzene. The benzene layer was separated, dried over sodium sulfate and evaporated. The residue was chromatographed on 6 g of silicagel using 20% ethyl acetate in methylene chloride. Crystallization of pure fractions from ether/hexane yielded 1,3 - dihydro - 5 - (2 - fluorophenyl) - 7 - iodo - 1 - methyl - 1,4 - benzodiazepin - 2 - one of melting point 106°—109°.

The starting material may be prepared as follows:

A mixture of 2.05 g of 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 1H - 1,4 - benzodiazepin - 2 - one 4-oxide, 20 ml of methylene chloride, 2 g of zinc dust and 5 ml of acetic acid was stirred at room temperature for 30 minutes. The filtered mixture was partitioned between methylene chloride and 10% aqueous sodium carbonate. The methylene chloride layer was washed with water, dried over sodium sulfate and evaporated. The residue was crystallized from (methylene chloride)/ether to yield crude 5 - (2 - fluorophenyl) - 1,3,4,5 - tetrahydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one. Pure material was obtained by recrystallization from (methylene chloride)/hexane and had a melting point of 171°—173°.

Example 9

A mixture of 10 ml of ethanol, 0.2 ml of diethyl azodicarboxylate and 0.4 g of 5 - (2 - fluorophenyl) - 1,3,4,5 - tetrahydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one was refluxed for 2 hours. After evaporation, the residue was chromatographed on 8 g of silicagel using (methylene chloride)/(ethyl acetate) (1:1). Crystallization of pure fractions yielded 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 106°—109°.

Example 10

A mixture of 0.55 g of 5 - (2 - fluorophenyl) - 1,3,4,5 - tetrahydro - 7 - iodo - 1 - methyl - 4 - (*p* - toluenesulfonyl) - 2H - 1,4 - benzodiazepin - 2 - one, 20 ml of benzene, 2 ml of *tert*butanol and 0.16 g of potassium *tert*butoxide was refluxed under nitrogen for 20 minutes. The reaction mixture was cooled, partitioned between water and ether. The organic layer was dried and evaporated. The residue was chromatographed on 6 g of silicagel using (ethyl acetate)/(methylene chloride) (1:1) (v/v). Crystallization of pure fractions from ether/

hexane yielded 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl -2H - 1,4 - benzodiazepin - 2 - one of melting point 106°—110°.

The starting material may be prepared as follows:

A mixture of 1 g of 5 - (2 - fluorophenyl) - 1,3,4,5 - tetrahydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one, 0.6 g of *p*-toluenesulfonyl chloride and 10 ml of pyridine was allowed to stand at room temperature overnight. After evaporation, the residue was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The organic phase was washed with 1-*N* hydrochloric acid and water, dried over sodium sulfate and evaporated. Crystallization of the residue from (methylene chloride)/ether and recrystallization from (methylene chloride)/ethanol yielded 5 - (2 - fluorophenyl) - 1,3,4,5 - tetrahydro - 7 - iodo - 1 - methyl - (*p* - toluenesulfonyl) - 2H - 1,4 - benzodiazepin - 2 - one of melting point 255°—258°.

Example 11

0.17 g of 5 - (2 - fluorophenyl) - 1,5 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one were dissolved in a solution of 50 mg sodium in 5 ml of anhydrous ethanol. This mixture was stirred at room temperature for 30 minutes under nitrogen, then acidified by addition of acetic acid and evaporated. The residue was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The methylene chloride layer was dried over sodium sulfate and evaporated. Crystallization of the residue from ether/hexane yielded 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 -benzodiazepin - 2 - one of melting point 106°—109°.

The starting material may be prepared as follows:

0.6 g of sodium borohydride were added to a solution of 4.1 g of 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one 4 - oxide in 100 ml of ethanol and 50 ml of tetrahydrofuran. The mixture was stirred at 40°—50° for 1.5 hours, concentrated *in vacuo* and crystallized by addition of water. The solid material was collected, dried and recrystallized from (methylene chloride)/hexane to yield 5 - (2 - fluorophenyl) - 1,3,4,5 - tetrahydro - 4 - hydroxy - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 216°—220°.

2 g of the compound prepared according to the preceding paragraph were allowed to stand at room temperature overnight in 20 ml of pyridine and 2 ml of acetic anhydride. The reaction mixture was evaporated and the residue crystallized from methanol to yield 1.5 g of 4 - acetoxy - 5 - (2 - fluorophenyl) - 1,3,4,5 - tetrahydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 172°—174°.

A mixture of 1g of the product obtained according to the preceding paragraph, 15 ml of ethanol and 5 ml of triethylamine was refluxed for 1 hour. The residue obtained upon evaporation was chromatographed on 20 g of silicagel using 10% ethyl acetate in methylene chloride for elution. The pure fractions were combined and evaporated. Recrystallization of the solid obtained from (methylene chloride)/hexane yielded 5 - (2 - fluorophenyl) - 1,5 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 191°—195.

Example 12

0.5 g of 4 - acetoxy - 5 - (2 - fluorophenyl) - 1,3,4,5 - tetrahydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one were dissolved in 10 ml of ethanol. 0.15 g of potassium *tert*butoxide were added and the mixture was refluxed for 15 minutes. After evaporation, the residue was partitioned between benzene and water. The benzene layer was dried and evaporated. Chromatography of the residue on 10 g of silicagel using ether/benzene (2:1) yielded 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 106°—110°.

Example 13

A solution of 0.45 g of methyl 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one 3 - carboxylate in 10 ml of methanol was degassed by nitrogen and stirred at room temperature for 3 hours after addition of 2 ml of 1-*N* aqueous sodium hydroxide solution. The reaction mixture was acidified by addition of 1-*N* hydrochloric acid, made alkaline with ammonia and extracted with ether. The ether extracts were dried over sodium sulfate and evaporated. Chromatography of the residue on 6 g of silica using (methylene chloride)/(ethyl acetate) (1:1) (w/w) yielded 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 106°—110°.

The starting material can be prepared as follows:

6.3 g of phosphorus pentachloride were added to a suspension of 8g of N - (benzyloxycarbonyl) - 2 - carbomethoxyglycine in 100 ml of methylene chloride cooled to minus 20°. The mixture was stirred at minus 20° to minus 15° for 30 minutes. 6.7 g of 2 - amino - 5 - iodobenzophenone were added followed by 100 ml of 10% aqueous sodium carbonate at 0° to 5°. The methylene chloride solution was separated.

washed twice with sodium carbonate solution, dried and evaporated. Crystallization of the residue from (methylene chloride)/hexane yielded 2 - [(benzyloxycarbonyl)amino] - 2 - carbomethoxy - 2′ - (2 - fluorobenzoyl) - 4′ - iodo - acetanilide of melting point 100°—103°.

20 ml of acetic acid conatining 30% hydrogen bromide were added to a solution of 5 g of the foregoing acetanilide in 50 ml of methylene chloride. The mixture was allowed to stand at room temperature for 4 hours and was then evaporated. The residue was slurried with ether and the crystalline solid was collected to yield a hydrobromide of melting point 188°—192° (decomposition).

3 g of the foregoing hydrobromide were partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The methylene chloride layer was dried over sodium sulfate, filtered and evaporated. Crystallization of the residue from (methylene chloride)/hexane yielded 2 - amino - carbomethoxy - 2′ - (2 - fluorobenzoyl) - 4′ - iodoacetanilide of melting point 120°—123°.

1.5 g of the amine thus obtained were refluxed in 50 ml of toluene containing 5 ml of acetic acid for 1.5 hours. The residue obtained after evaporation of the reaction mixture was crystallized from (methylene chloride)/ether to yield methyl 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 2H - 1,4 - benzodiazepin - 2 - one 3 - carboxylate of melting point 230°—236° (decomposition).

0.88 g of the foregoing ester were dissolved in 20 ml of dimethylformamide and the solution was cooled to minus 20°. 0.3 g of potassium *tert*butoxide were added and, after stirring for 5 minutes, 0.2 ml of dimethyl sulfate were added. The temperature was allowed to reach 0°. The reaction mixture was acidified with acetic acid and poured into ice-water. The precipitated product was collected and dissolved in methylene chloride. The solution was dried over sodium sulfate, filtered and evaporated. Crystallization of the residue from ether/hexane yielded methyl 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one - 3 - carboxylate melting at 135°—139° after recrystallization from (methylene chloride)/hexane.

Example 14

A mixture of 0.4 g of 5 - (2 - fluorophenyl) - 1,3,4,5 - tetrahydro - 4 - hydroxy - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one, 5 ml of pyridine and 0.2 ml of phosphorus oxychloride was refluxed for 5 minutes and evaporated under reduced pressure. The residue was partitioned between benzene and 10% aqueous sodium carbonate solution. The organic layer was dried over sodium sulfate and evaporated. Chromatography on 6 g of silicagel using 10% (v/v) ethyl acetate in methylene chloride yielded 5 - (2 - fluorophenyl) - 1,5 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 188°—192° after crystallization from hexane/(methylene chloride). Later eluated fractions yielded, after crystallization from ether/hexane, the isomeric 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one of melting point 102°—106°.

The following Examples illustrate pharmaceutical preparations containing the benzodiazepine derivatives provided by the invention:

Example A
Capsule Formulation

	Per Capsule
5-(2-fluorophenyl)-1,3-dihydro-7-iodo-1-methyl-2H-1,4-benzodiazepin-2-one	10 mg
Lactose	165 mg
Corn Starch	30 mg
Talc	5 mg
Total Weight	210 mg

Procedure:

5 - (2 - Fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one, lactose and corn starch were mixed in a suitable mixer. The mixture was further blended by passing it through a comminuting machine. The blended powder was returned to the mixer, the talc added and blended thoroughly. The mixture was filled into hard shell gelatin capsules on a capsulating machine.

Example B
Parenteral Formulation

	per ml
5-(2-fluorophenyl)-1,3-dihydro-7-iodo-1-methyl-2H-1,4-benzodiazepin-2-one	5.1 mg
Benzyl Alcohol	0.015 ml
Propylene Glycol	0.5 ml
Ethyl Alcohol (Anhydrous)	0.1 ml
Disodium Edetate*	0.1 mg
Sodium Acetate Trihydrate	1.4 mg
Acetic Acid (Glacial)	0.6 mg
Sodium Hydroxide, 10% Solution *q.s.* to pH 6.0	
Water for Injection *q.s.* to	1.0 ml

Procedure (For 5000 ml).

5 - (2 - Fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one was added to propyleneglycol and benzyl alcohol and heated to 40°C with stirring to effect solution. After the solution had cooled to 30°C or below, the ethyl alcohol and disodium edetate, sodium

acetate and glacial acetic acid were dissolved in approximately 500 ml of water for injection and added to the solution. The solution was adjusted to pH 6.0 with 10% sodium hydroxide and brought to volume with water for injection. The solution was filtered through a sterile candle and filled into sterile 2 ml ampoules which flushed with nitrogen and sealed. They were then autoclaved at 0.7 atmospheres for 30 minutes.

*Disodium salt of ethylenediaminetetraacetic acid.

Example C
Tablet Formulation

	Per Tablet
5-(2-fluorophenyl)-1,3-dihydro-7-iodo-1-methyl-2H-1,4-benzodiazepin-2-one	100 mg
Lactose	202 mg
Corn Starch	80 mg
Prehydrolyzed Corn Starch	20 mg
Calcium Stearate	8 mg
Total Weight	410 mg

Procedure:

5 - (2 - Fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one, lactose, corn starch and prehydrolyzed corn starch were blended in a suitable mixer. The mixer was granulated to a heavy paste with water and the moist mass was passed through a comminuting machine. It was then dried overnight at 45°C. The dried granules were passed through a comminuting machine and transferred to a suitable mixer. The calcium sterate was added and mixed until uniform. The mixture was compressed at a tablet weight of 410 mg.

Example D
Tablet Formulation

	Per Tablet
5-(2-fluorophenyl)-1,3-dihydro 7-iodo-1-methyl-2H-1,4-benzodiazepin-2-one	25 mg
Dicalcium Phosphate Dihydrate (Unmilled)	175 mg
Corn Starch	24 mg
Magnesium Stearate	1 mg
Total Weight	225 mg

Procedure:

5 - (2 - Fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one and cornstarch were mixed together and passed through a comminuting machine. This premix was then mixed with dicalcium phosphate and one-half of the magnesium stearate, passed through a comminuting machine and slugged. The slugs were passed through a comminuting machine and the remaining magnesium stearate was added. The mixture was mixed and compressed.

Example E
Capsule Formulation

	Per Capsule
5-(2-Fluorophenyl)-1,3-dihydro-7-iodo-1-methyl-2H-1,4-benzodiazepin-2-one	50 mg
Lactose	125 mg
Corn Starch	30 mg
Talc	5 mg
Total Weight	210 mg

Procedure:

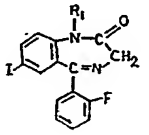
5 - (2 - Fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one was mixed with lactose and corn starch in a suitable mixer. The mixture was further blended by passing through a comminuting machine. The blended powder was returned to the mixer, the talc added and blended thoroughly. The mixture was filled into hard shell gelatin capsules on a capsulating machine.

Example F

In an analogous manner to the procedures described in Examples A to E, pharmaceutical formulations can be prepared using 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 2H - 1,4 - benzodiazepin - 2 - one as the active ingredient.

WHAT WE CLAIM IS:—

1) Compounds of the general formula



(I)

wherein R_1 represents a hydrogen atom or the methyl group,

and acid addition salts thereof.

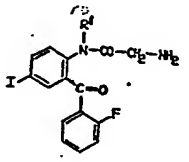
2) 5 - (2 - Fluorophenyl) - 1,3 - dihydro - 7 - iodo - 2H - 1,4 - benzodiazepin - 2 - one.

3) 5 - (2 - Fluorophenyl) - 1,3 - dihydro - 7 - iodo - 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one.

4) A pharmaceutical preparation comprising a compound of formula I in claim 1 or a pharmaceutically acceptable acid addition salt thereof in association with a compatible pharmaceutical carrier.

5) A process for the manufacture of the benzodiazepine derivatives claimed in claim 1, which process comprises

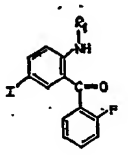
a) cyclizing a compound of the general formula



(II)

wherein R_1 has the significance given in claim 1, or

b) treating a compound of the general formula

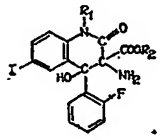


(III)

wherein R_1 has the significance given in claim 1,

with glycine or an ester thereof, or

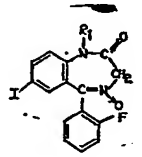
c) effecting ring expansion and acid hydrolysis under aqueous conditions of a compound of the general formula



(IV)

wherein R_1 has the significance given in claim 1, and R_2 represents a lower (C_1—C_4) alkyl group, or

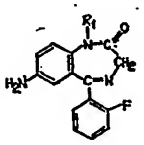
d) deoxidizing a compound of the general formula



(V)

wherein R_1 has the significance given in claim 1, or

e) subjecting the diazonium salt of a compound of the general formula

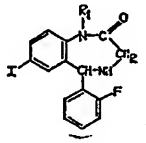


(VI)

wherein R_1 has the sigfnificance given in claim 1,

to a SANDMEYER-type replacement, or

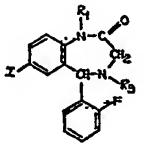
f) oxidizing or dehydrogenating at the 4, 5-bond a compound of the general formula



(VII)

wherein R_1 has the significance given in claim 1, or

g) converting a compound of the general formula

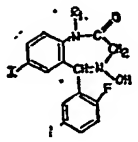


(VIII)

wherein R_1 has the significance given in claim 1 and R_3 represents a halogen atom or an acyl group,

into a corresponding 4,5 - dehydro compound of formula I in claim 1 by treatment with a strong base, or

h) dehydrating a compound of the general formula

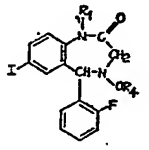


(IX)

wherein R_1 has the significance given in Claim 1,

to yield a corresponding 4,5-dehydro compound of formula I in claim 1, or

i) treating a compound of the general formula

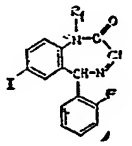


(X)

wherein R_1 has the significance given in claim 1 and R_4 represents an acyl group,

with a base to yield a corresponding 4,5-dehydro compound of formula I in claim 1, or

j) rearranging a compound of the general formula

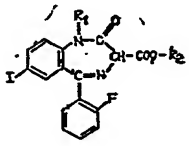


(XI)

wherein R_1 has the significance given in claim 1,

to a corresponding 4,5-dehydro compound of formula I in claim 1 or

k) saponifying and decarboxylating a compound of the general formula



(XII)

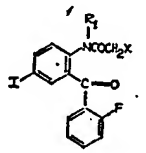
wherein R_1 has the significance given in claim 1 and R_2 has the significance given earlier in this claim, or

l) methylating the compound of formula I in claim 1 wherein R_1 represents a hydrogen atom to yield the compound of formula I in claim 1 wherein R_1 represents the methyl group and, if desired,

m) converting a compound of formula I into an acid addition salt.

6) A process as claimed in claim 5, wherein the cyclization of a compound of formula II is effected by slight heating in the presence of an inert organic solvent.

7) A process as claimed in claim 5 or claim 6, wherein the compound of formula II is prepared from a compound of the general formula



(XIII)

wherein R_1 has the significance given in claim 1 and X represents a leaving atom or group, a carbobenzoxyamino group or a phthalimido group.

8) A process as claimed in claim 7, wherein the compound of formula II is not isolated but is cyclized *in situ* under the conditions employed.

9) A process as claimed in claim 7 or claim 8, wherein a compound of formula XIII wherein X represents a leaving atom or group is treated with ammonia.

10) A process as claimed in 9, wherein said leaving atom or group is a halogen atom of an alkylsulfonyloxy or arylsulfonyloxy group.

11) A process as claimed in claim 7 or 8, wherein the carbobenzoxy group is removed from a compound of formula XIII wherein X represnts a carbobenzoxyamino group.

12) A proecss as claimed in claim 11, wherein the carbobenzoxy group is removed by treatment with hydrogen bromide in acetic acid.

13) A process as claimed in claim 7 or claim 8, wherein a compound of formula XIII wherein X represents a phthalimido group is treated with hydrazine.

14) A process as claimed in claim 5, wherein the treatment of a compound of formula III with glycine or an ester thereof is effected under acidic conditions.

15) A process as claimed in claim 5, wherein the deoxidation of a compound of formula V is effected by means of a phosphorus trihalide, hydrogenation in the presence of a hydrogenation catalyst or zinc in acetic acid.

16) A process as claimed in claim 5, wherein the diazonium salt of a compound of formula VI is treated with an alkali metal iodide or cuprous iodide.

17) A process as claimed in claim 5, wherein the oxidation or dehydrogenation of a compound of formula VII is effected with oxygen, manganese dioxide, bromide, chlorine or an azo dicarboxylic acid ester.

18) A process as claimed in claim 5, wherein a compound of formula VIII or X is treated in an anhydrous medium with an

alkali metal hydride, an alkali alkoxide, an alkali amide or triethylamine.

19) A process as claimed in claim 5, wherein a compound of formula IX is treated with thionyl chloride, phosphorus oxychloride or a carbodiimide.

20) A process as claimed in claim 5, wherein a compound of formula XI is treated with a base.

21) A process as claimed in claim 20, wherein the base is an alkali alkoxide, an alkali hydride or triethylamine.

22) A process as claimed in claim 5, wherein a compound of formula XII is hydrolysed under alkaline conditions and wherein the decarboxylation is accomplished by allowing a solution of the hydrolysed compound to stand, or by heating or acidifying this compound in solution.

23) A process as claimed in claim 5, wherein a compound of formula XII is treated with an acid.

24) A process as claimed in claim 5, wherein the compound of formula I wherein R_1 represents a hydrogen atom is converted into a 1-alkali metal salt and such salt is treated with a methylating agent.

25) A process as claimed in any one of claim 5 to 23 inclusive, wherein 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo - 2H - 1,4 - benzodiazepin - 2 - one is manufactured.

26) A process as claimed in any one of claims 5 to 24 inclusive, wherein 5 - (2 - fluorophenyl) - 1,3 - dihydro - 7 - iodo 1 - methyl - 2H - 1,4 - benzodiazepin - 2 - one is manufactured.

27) A process for the manufacture of the benzodiazepine derivatives claimed in claim 1, substantially as described with reference to Examples 1 to 14.

28) Benzodiazepine derivatives as claimed in claim 1, when manufactured by the process claimed in any one of claims 5 to 27 inclusive.

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